Patterns of conduction impairment in experimental allergic neuritis. An electrophysiological and histological study

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Abstract
Electrophysiological and histological studies of peripheral nerve were performed in 24 Lewis rats with experimental allergic neuritis (EAN) in which disease had been induced by a single myelin and adjuvant inoculation in one footpad. Demyelination was demonstrated in transverse nerve sections from ventral roots, proximal sciatric nerves and also in distal plantar nerves. Histological and electrophysiological assessments showed that injected limbs were more affected than uninjected limbs. Neurophysiological studies demonstrated two distinct patterns of conduction failure based upon proximal/distal compound muscle action potential (CMAP) amplitude ratios in both un.injected and injected limbs. Slightly more than half of all nerve trunks showed a mildly reduced distal CMAP amplitude irrespective of stimulus origin. The rest displayed a more severe reduction of distal amplitude that was length-dependent, becoming smaller with proximal stimulation. Histological lesions in plantar nerves were often more severe than those in proximal sciatric nerves or ventral roots. Axonal degeneration was an uncommon finding.

This study has demonstrated patterns of peripheral nerve conduction impairment similar to those reported in patients with inflammatory demyelinating neuropathy. Moreover, it has shown that a low distal CMAP amplitude may result from demyelination of distal motor nerve segments and not necessarily from axonal degeneration.

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Experimental allergic neuritis (EAN) is recognised as the animal model of human Guillain-Barré syndrome (GBS) and both diseases share similar clinical, pathological and electrophysiological features. Prognostic characteristics of GBS are poorly identified. Two distinct patterns of nerve conduction abnormalities have been identified in GBS at least in the early phases of disease. The first is a length-dependent reduction of the distal compound muscle action potential (CMAP) with relative sparing of sensory potentials that may, when observed in the absence of excessive dispersion, be related to a widespread distribution of demyelinating lesions. The second is a simple reduction of the distal CMAP with little variation in amplitudes generated at different levels of the nerve and which features both motor and sensory nerve impairment. More recently, similar patterns of conduction abnormalities have been identified in chronic inflammatory demyelinating polyneuropathy (CIDP).

A recent review of electrophysiological data taken from the North American study of GBS found that mean distal CMAP amplitude was the most powerful predictor of clinical outcome following treatment by plasma exchange. Furthermore, low distal CMAP amplitudes were associated with predispositions to severe disease with increasing probability of poor recovery, a finding that suggests the presence of axonal degeneration. This conclusion, however, which has important consequences for the design and instigation of treatment regimes is superficially at variance with other detailed studies, in which a low distal amplitude resulted possibly from distal demyelination.

This investigation was designed to assess whether demyelination in the distal regions of the peripheral nervous system (PNS) is a common feature of EAN and whether distinct patterns of nerve conduction abnormalities can be identified in EAN similar to those in human GBS and CIDP.

Materials and methods
Induction of EAN
Twenty four male Lewis rats (body weight 250–320 g) on a standard diet of commercial animal chow and water ad libitum were inoculated with a water-in-oil homogenate of bovine nerve root myelin, sterile saline and Freund’s complete adjuvant. The myelin was prepared by discontinuous sucrose density gradient centrifugation similar to the method of Norton and Poduslo (1973). The inoculum was prepared by mixing myelin, sterile saline, Freund’s incomplete adjuvant (CSL Melbourne, Australia) and Mycobacterium bovis strain AN5 (CSL) in the ratio of 50 mg: 1 ml: 1 ml: 6 mg and homogenising by repeated expulsion between glass syringes coupled with a miniature three way tap. Animals were then anaesthetised using halothane/O2 and each given a single subcutaneous injection of 0.1 ml of inoculum into the right footpad. The left footpad remained uninjected. Animals were assessed daily for signs of EAN.

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Electrophysiologic studies
Animals underwent electrophysiological measurements at day 0 before disease induction and at day 18 post-inoculation. Following anaesthesia using halothane/O₂, the sciatic nerve was stimulated both proximally and distally through paired stainless steel needle electrodes. One pair was placed to lie alongside the sciatic nerve at the sciatic notch and the other pair was placed at the ankle. The compound muscle action potential was recorded from the small muscles of the feet by another pair of stainless steel needle electrodes. Supramaximal rectangular pulses of 50 ms duration were delivered from an isolated voltage stimulator (Devices Mk IV) triggered by a microcomputer (Apple Ile) at no less than 1 second intervals. Submaximal stimulation strength was used to locate the optimum stimulus electrode site. Signals were pre-amplified by a high input impedance differential amplifier and further amplified to provide an appropriate input for an analogue to digital converter (Applied Engineering 12 bit A/D). Responses were stored and analysed within the microcomputer, displayed on a videomonitor and later stored on floppy disc. For both the injected and uninjected side of each animal proximal and distal latencies were measured using time-intervals from the stimulus artifact to the first negative deflection from baseline. Proximal conduction velocities were calculated using the distances from the sciatic notch to the ankle and the differences between proximal and distal latencies. Amplitudes of the CMAP from both proximal and distal stimulation were also determined. The ratio of CMAP amplitudes recorded from proximal stimulation to that from distal stimulation was calculated as the R ratio.

Histological studies
Directly after completion of electrophysiological measurements on day 18 post-inoculation, animals were anaesthetised with an overdose of pentobarbitone sodium, perfused via the descending aorta with sterile saline, 2.5% paraformaldehyde and 4% glutaraldehyde in phosphate buffer. After laminectomy the 4th and 5th lumbar nerve roots together with a 1-0 cm segment of the proximal sciatic nerve at the sciatic notch from each side were removed. For distal nerve sections five millimetre samples of lateral and medial plantar nerves just proximal to the heel were also taken from each side. For transverse sections, the nerves were post-fixed in Dalton’s chrome osmium solution, dehydrated in graded concentrations of ethanol and embedded in Spurr’s resin. Cross-sections 1 μm thick were cut, stained with toluidine blue and examined by light microscopy.

Histological changes within nerves were assessed in a semi-quantitative fashion by the assignment of scores based on a 5 grade histological classification system as follows: 0 – normal, 1 – mild cellular infiltrate adjacent to vessels, 2 – cellular infiltrate and demyelination adjacent to vessels, 3 – cellular infiltrate and demyelination extending into nerve parenchyma, 4 – cellular infiltration and demyelination throughout section, 5 – widespread demyelination with marked axonal loss. A score was assigned from the examination of whole sections by 2 examiners one of whom was unaware of the source of the sections.

Results

Clinical features
In all animals inoculations produced mild to moderate swelling at the site of injection in the footpad. No obvious swelling could be observed in any uninjected foot.

All 24 animals inoculated with myelin developed clinical signs of EAN between days 10 and 13 post inoculation. A flaccid tail initially developed into a mild to moderate paraparesis in the majority of animals. A small minority became severely paralysed. None developed quadriparesis within the 18 day timeframe of investigation. Although most animals showed mild signs of discomfort from the inoculation, no clear differences in clinical weakness could be observed between the injected limb and the uninjected limb in any animal.

Electrophysiological Studies

Uninjected Limb
At day 18 post-inoculation measurements of CMAP amplitudes with proximal (hip) stimulation in the uninoculated limbs of all 24 animals revealed a mean 28% decrease compared with control pre-inoculation values (2-tailed paired Student’s t test, p < 0.005). Distal (ankle) stimulation produced a smaller 12% reduction in CMAP amplitudes (p < 0.005) (table 1) and the proximal/distal CMAP amplitude ratios (R ratios) were reduced by an average of 21% from control pre-inoculation ratios (p < 0.05). In contrast there were no significant changes in action potential latencies from distal stimulation and no changes in proximal conduction velocities.

Injected Limb
Nerve conduction measurements in myelin/FGA inoculated limbs revealed more severe conduction abnormalities compared with non-injected limbs. CMAP amplitudes produced by proximal stimulation revealed a mean 62% reduction from control values (p < 0.001).

Comparisons between changes in amplitude expressed as percentage changes from control pre-inoculation readings showed a significantly greater reduction on the injected side compared with the uninjected side (p < 0.001) Action potential amplitudes generated by ankle stimulation were reduced in a similar fashion by 54% compared with control readings (p < 0.001). This decrease was also statistically significantly larger on the injected side compared with the 12% reduction on the uninjected side (p < 0.001). Also in contrast the injected limb showed significant increases in distal latencies (11%, p < 0.001) and decreases in proximal conduction velocities (−12%, p < 0.005). The R ratio was also significantly decreased from pre-inoculation values (−37%, p < 0.001), the injected limb
of conduction impairment based upon the behaviour of the proximal/distal CMAP amplitude ratios. In some nerve trunks the R ratio was reduced from control values, indicating a length-dependent reduction (LDR) in CMAP amplitudes induced by nerve lesions between proximal and distal stimulating electrodes. In others, a simple reduction (SR) in distal amplitudes was observed with the R ratio remaining relatively unchanged. Individual sciatic trunks regardless of side were therefore grouped according to the following criteria. Nerves displaying length-dependent reductions were defined as those in which the R ratio decreased to more than the lowest mean control value for the ratio for all 24 animals minus 2 standard deviations (table 1), that is, < 0·73. Figure 1 shows muscle action potentials from the uninoculated limb of animal 103 whose sciatic nerve trunk was assigned to the LDR group. The rest having ratios equal to or above this cutoff value were defined as having a simple reduction in CMAP amplitudes. Figure 2 shows the action potentials from animal 87 whose sciatic nerve trunk in an inoculated limb was assigned to the SR group. Electrophysiological data from nerves thus grouped are summarised in table 2.

Twenty six out of 48 sciatic trunks studied displayed simple reductions in CMAP amplitudes. This SR group was made up of 15 nerves from injected and 11 from uninjected limbs. The 22 sciatic trunks in the LDR group were made up of 13 nerves from injected and 9 from uninjected limbs. R ratios were, by definition, unchanged from control values in the SR group and significantly reduced in the LDR group (p < 0·001). The difference in ratio averages between the 2 groups was prominent in magnitude [0·86 (0·06) vs 0·31 (0·21)] and highly statistically significant (p < 0·001) implying adequate criteria for group separation.

In the SR group, both proximal and distal CMAP amplitudes were similarly significantly reduced from control (−16·7%, p < 0·005; −17·7%, p < 0·001 respectively) indicating that an unchanged R ratio was not due to a lack of disease. However, changes in CMAP amplitudes were generally mild. Only 3 out of 26 nerves in the SR group showed decreases of ≥ 50% of control amplitudes. Proximal conduction velocities were unaltered from control

|Table 1 | Nerve conduction data from left uninjected and right injected limbs |
|--------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|        | Uninjected limb n = 24     | Injected limb n = 24        |
| Mean (SD) | Day 0 | Day 18 | % change | Day 0 | Day 18 | % change |
| Proximal amplitude (mV) | 15-4 (2·28) | 10·9 (5·73) | -28-1 (56·7) | 15·8 (2·30) | 5·92 (5·83) | -62·4 (37·0) |
| Distal amplitude (mV) | 17·7 (2·59) | 15·4 (3·56) | -11·9 (18·3) | 19·0 (2·08) | 8·87 (6·60) | -5·3 (33·7) |
| R ratio | 0·87 (0·03) | 0·69 (0·30) | -20·8 (34·4) | 0·83 (0·05) | 0·52 (0·31) | -37·1 (37·6) |
| Distal latency (ms) | 1·32 (0·10) | 1·38 (0·16) | 4·76 (13·0) | 1·28 (0·07) | 1·42 (0·19) | -1·0 (14·5) |
| Conduction velocity (m/s) | 46·3 (4·46) | 45·2 (6·56) | -1·81 (14·5) | 47·1 (4·41) | 41·2 (8·52) | -12·2 (17·1) |

Paired t test
Day 0 vs day 18
p < 0·05
p < 0·005
p < 0·001

Figure 1. CMAPs from hip and ankle stimulation of the left uninoculated limb of animal 103 at day 0 (A) and day 18 (B). Note reduction of distal CMAP amplitude with proximal stimulation.
values as were distal latencies.

In the LDR group, proximal amplitudes were decreased considerably from control values (−79–0%, p < 0.001) and significantly more so than for the SR group (p < 0.001). Distal amplitudes were also decreased (−50–5%, p < 0.001) and this decrease from control was again greater in the LDR group than in the SR group (p < 0.001). In contrast to the SR group, ankle latencies were significantly increased in the LDR group (p < 0.001) and comparisons of percentage changes in latencies between SR and LDR groups confirmed that CMAPs were more delayed (3–9% vs 12–6% respectively, p < 0.05). Also unlike the SR group, proximal conduction velocities were also decreased (p < 0.001).

**Histological studies**

Table 3 represents a summary of the results from histological scoring of cellular infiltration, demyelination and axonal degeneration in transverse nerve sections from 16 animals. Peripheral nerve abnormalities were found in all the different areas sampled including the most distal nerve regions. In all but one animal lesions in ventral roots, left and right proximal sciatric nerves were of a mild to moderate character (scores 1–3). The majority of animals showed lesions in plantar nerve samples and here there was a greater range in the severity of lesions compared with ventral roots or proximal sciatric nerves. A total of 7 plantar nerves, 2 from uninjected and 5 from injected sides showed severe nerve lesions (scores ≥ 4) featuring overt cellular infiltration and demyelination. From these, 2 nerves from injected limbs also showed marked axonal degeneration (score 5).

**Comparisons between injected and uninjected sides**
The summary of histological results in table 3 suggests that lesions in proximal sciatric nerves appeared greater in severity in injected limbs compared with uninjected limbs. This concurs with electrophysiological data in table 1 showing greatest changes in proximal nerve conduction on injected sides. Histological scoring of distal plantar nerves indicated that lesions here were also generally more developed on the injected side compared with the uninjected side (table 3). Score 1 was the most frequently assigned score for distal nerves in the left uninjected side with only 2 animals showing severe lesions. In contrast, the most assigned score for the injected side was 2 with 5 animals showing severe lesions. Also, although in each

**Table 2 Nerve conduction data from sciatric trunks grouped according to R ratio†**

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>Simple reduction n = 26</th>
<th>Length-dependent reduction n = 22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 18</td>
</tr>
<tr>
<td>Proximal amplitude (mV)</td>
<td>15.3 (2.27)</td>
<td>12.7 (4.59)</td>
</tr>
<tr>
<td>Distal amplitude (mV)</td>
<td>18.0 (2.50)</td>
<td>14.8 (5.04)</td>
</tr>
<tr>
<td>R ratio</td>
<td>0.85 (0.04)</td>
<td>0.86 (0.06)</td>
</tr>
<tr>
<td>Distal latency (ms)</td>
<td>1.32 (0.09)</td>
<td>1.37 (0.18)</td>
</tr>
<tr>
<td>Conduction velocity (m/s)</td>
<td>47.5 (4.57)</td>
<td>47.4 (4.54)</td>
</tr>
</tbody>
</table>

Paired t test

Day 0 vs day 18 Simple reduction vs Length-dependent reduction
p < 0.05
p < 0.005 ***
p < 0.001 ***

†—see grouping criteria see Results.

**Figure 2** CMAPs from hip and ankle stimulation of the right inoculated limb of animal 87 at day 0 (A) and day 18 (B). Note simple reduction of distal CMAP amplitude irrespective of stimulus origin.
of 4 animals lesions were scored as equal in severity in plantar nerves from both injected and uninjected limbs, in 11 of the remaining 12 animals nerves from injected limbs scored higher in blind assessments than those from uninjected limbs. These histological observations concur with electrophysiological findings in table 1 showing greater changes in distal nerve conduction in injected limbs compared with uninjected limbs. Figures 3 and 4 show severe lesions in transverse nerve sections of the plantar nerve from injected limbs of animals 29 and 137 respectively. Distal CMAP amplitudes in these animals were considerably reduced compared with control readings. Amplitudes were decreased by 88% and 80 respectively. In these particular animals distal lesions feature severe demyelination without significant axonal degeneration.

Comparisons between SR and LDR groups
A summary of histological data presented in Table 4 suggests that lesions were more severe in nerve trunks showing length-dependent reductions in CMAP amplitudes and these agree with the electrical studies. This was confirmed for the distal regions of the nerves by a statistically significant difference in scores assigned to plantar nerves in the LDR group compared with those in the SR group (Mann-Whitney U test, p < 0.05). Similar testing for proximal sciatic nerve data failed to confirm a difference between the SR and DR groups. In the SR group, 5 proximal sciatic nerves were scored 2 and in plantar nerves only 1 was scored 3 and 1 was scored 4. No nerves showed marked axonal degeneration. In contrast in the LDR group, 1 proximal sciatic and 4 plantar nerves were severely demyelinated and scored 4. Two plantar nerves showed severe demyelination as well as marked axonal degeneration.

Discussion
This study confirms the findings of previous electrophysiological studies that CMAPs of peripheral nerves in animals with EAN are characteristically reduced in amplitude and delayed10 in a similar fashion to peripheral nerves in GBS.10-13 Furthermore, this study shows that nerve lesions detectable by electrophysiological and histological examination are a common feature in the distal regions of the PNS in rats with EAN. In animals injected with myelin/IFA in only a single footpad, lesions were detected in the plantar nerves from both inoculated and uninoculated limbs.

In the majority of animals both proximal and distal peripheral nerves were more severely affected in the injected limb compared with the uninjected limb. This observation was based upon electrical studies noting significant differences in proximal and distal CMAP amplitudes, latencies and conduction velocities, and also histological studies in which lesions in transverse nerve sections were assessed in a semi-quantitative fashion. Interestingly, the more severe conduction impairment in inoculated limbs was not simply confined to the distal regions of the PNS in closest proximity to the inoculation site. Whereas distal nerves on inoculated sides were more affected than distal nerves on uninoculated sides, so were more proximal nerve sites well removed from

Table 4 Mean histological scores for different levels of grouped sciatic trunks

<table>
<thead>
<tr>
<th>Score</th>
<th>Simple reduction</th>
<th>Length-dependent reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=17</td>
<td>n=15</td>
</tr>
<tr>
<td>Proximal sciatic</td>
<td>0.9 (0.8)</td>
<td>1.6 (1.1)</td>
</tr>
<tr>
<td>Distal plantar</td>
<td>1.3 (1.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

1—For score criteria see Methods.
2—Mann-Whitney U test p < 0.05.
the site of injection in the foot. This was indicated by differences between sides in proximal conduction velocities and R ratios. Hence, the finding of neurophysiological abnormalities in injected limbs cannot be ascribed simply to gait artifact from foot swelling and nerve compression. Indeed, to avoid this possibility distal nerve segments sampled for histology were removed just proximal to the heel where no obvious swelling could be detected as at the injection site in the footpad. However, the extent to which a local swelling artifact suggested by significantly decreased distal amplitudes contributed to conduction impairment over the length of the sciatic trunk in injected limbs suggested by significantly altered proximal conduction velocities, distal latencies and R ratios is difficult to quantify.

This increased severity of lesions detected electrophysiologically and histologically in inoculated limbs compared with uninoculated limbs has not been reported previously. The types and doses of antigen and the sites of antigen inoculation for the induction of EAN have varied considerably since the initial study of EAN by Waksman and Adams\(^{18,19}\) and only relatively recently have links between methods of disease induction and severity and duration of EAN been investigated.\(^{18,19}\) These previous studies have shown a correlation between antigen dose and severity and chronicity of disease between animals. A similar effect appears to be acting locally within individual animals in this study.

Histological nerve lesions were also reported in both injected and uninjected limbs in the study of Hahn et al.\(^{17}\) but in contrast to this study the authors were unable to detect differences between sides. In their dose-response study, the inoculation of Lewis rats with 2-5 mg of myelin, an identical myelin dose as used here, produced lesions in sciatic nerves featuring severe inflammatory infiltration, extensive oedema, scattered demyelination with severe axonal destruction. No differences could be detected between proximal and distal sciatic nerves. Extensive demyelination with axonal degeneration was also reported in lumbar roots. These findings contrast with those presented here of mild to moderate lesions in ventral roots and both left and right proximal sciatic nerves with no significant axonal degeneration. Also in contrast, electrophysiological measurements and histological assessments revealed differences in nerves between uninjected and injected limbs and between proximal and distal nerve sites. The disease induced by Hahn et al (1988)\(^{17}\) with 2-5 mg of myelin per animal appears more severe than that produced in our study. Although the myelin dose is identical, the disease inducing potential of the inoculum could differ through subtle differences in methods of myelin isolation, the type of FCA and the dose of mycobacteria. Details of FCA and mycobacteria dose were not reported by Hahn et al.

The detection of differences in nerve conduction and histological lesions within different peripheral nerve sites in animals with EAN may depend upon the induction of a moderate disease in which axonal degeneration is not a feature. Thus in contrast to a severe disease in which lesions could be widespread throughout the PNS, nerve abnormalities may depend on initial susceptibility therefore presenting measurable regional differences in nerve function and pathology.

Nerve abnormalities were demonstrated in this study by either electrophysiology, histology or both at all levels investigated in the PNS. However, 2 different patterns of nerve conduction abnormalities emerged in these EAN animals indicating differences within and between animals in the severity and position of lesions. Two groups could be distinguished at the approximate nadir of their neuropathy on the basis of the proximal/distal CMAP amplitude ratios. One group possessed R ratios basically unchanged from control pre-inoculation values. The other group was distinguishable by significantly lowered R ratios. Although not equal in number, nerves from both injected and uninjected limbs were found in either group, indicating that factors in addition to the site of inoculation determine the site of lesions and these patterns of conduction impairment.

The finding of distal demyelination in both SR and LDR groups may further lend support to the notion that distal nerves are just as susceptible to demyelination if not more so than more proximal nerve sites. Predisposition to the formation of nerve lesions is thought to be linked to the permeability properties of the perineurium and endoneurial vessels in certain regions of the PNS. Olsson\(^ {18}\) has noted that pathological alterations in the PNS are generally more severe in areas where the blood nerve barrier is more permeable, for example, dorsal root ganglia, spinal roots and also the most distal regions of nerves where macro-molecular and ionic tracers have been shown to have relatively free access to the endoneurium.\(^ {19-21}\) In this study both proximal and distal nerves were more severely affected in the LDR group of rats showing significant decreases in the R ratio. This conclusion was based upon both electrophysiological as well as histological observations. Demyelinating lesions could have a tendency to develop initially in distal nerves and nerve roots and in mildly affected animals be confined to those areas. A more severe autoimmune neuropathy could then be characterised by lesions of increased severity in distal nerves, nerve roots and in addition the formation of lesions between these sites in the sciatic nerve with electrophysiological measurements showing a length-dependent reduction of LAP amplitudes and reduced R ratios.

These 2 patterns of conduction impairment in EAN based upon the proximal/distal CMAP amplitude ratio are similar to those which have been previously reported in human GBS\(^ {2}\) and CIDP.\(^ {4}\) Findings in GBS patients of little change in distal CMAP amplitude with more proximal stimulation have been attributed to either distal demyelination or axonal degeneration. Data from EAN rats in the present study
are similar to those from human GBS and CIDP patients and show that some individuals display simple reductions in distal CMAP amplitudes with little change in the proximal/distal amplitude ratios and also that there is a considerable variation between individuals in the magnitude of the changes in distal amplitudes. Examination of transverse nerve sections of the PNS from rats in the SR group revealed lesions with mild to moderate cellular infiltration and demyelination, and occasional animals showing severe demyelination in distal nerves. Of note in this SR group was an absence of axonal degeneration even in the most severely affected distal nerves.

Cornblath et al. have shown that in GBS patients a low mean distal CMAP amplitude (0–20% of the lower limit of normal) is a useful prognostic sign of poor outcome. These data, derived from the large group of patients involved in the North American Study of Plasmapheresis do not mean that in individual cases a low distal CMAP amplitude necessarily indicates axonal degeneration and poor outlook. This point is emphasised by this experimental study in which significant reductions in distal CMAP amplitude were found in plantar nerves and were correlated with distal demyelination upon histological examination. It was of particular interest that distal demyelination was identified in a large number of animals in this study and only in 2 nerves was significant axonal degeneration seen. These findings suggest that further studies of distal motor nerve fibres (that is, intramuscular nerves) may be indicated in patients with inflammatory demyelinating neuropathy.

In conclusion, although clinical outcome was not measured in this study and therefore could not be correlated with distal CMAP amplitudes as in the study of PE in GBS, the finding of demyelination in rat distal nerve sections with only a minority of severely affected nerves also showing marked axonal degeneration shows that in this form of EAN at least, low distal CMAP amplitudes do not necessarily indicate a significant loss of axons.

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